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## Fluid loading responsiveness

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## Chapter 7

### **Partitioning the resistances along the vascular tree: effects of dobutamine and hypovolemia in piglets with an intact circulation**

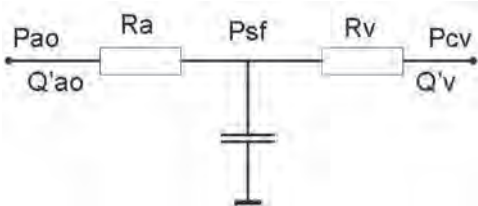
Bart Geerts, Jacinta Maas, Leon Aarts, Michael Pinsky and Jos Jansen  
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The hemodynamic effects of therapeutic interventions have been extensively studied on isolated arterial, venous or heart models either in vitro or in vivo. Although, intact circulation models have been used before, they are often limited to only one study characteristic; i.e. heart function, venous capacitance, (un)stressed volume, vascular compliance, mean systemic filling pressure or venous resistance [1]. None of these models is applicable in ICU patients and none was used to determine the coherent characteristics of the venous and arterial vasculature and heart function. Since arteries, veins and heart operate in concert, we developed an integrated in vivo model, applicable in patients, based on Guytonian physiology.

We modelled the systemic circulation with one resistor upstream ( $R_a$ ) and one resistor downstream ( $R_v$ ) of mean systemic filling pressure ( $P_{msf}$ ) (Figure 1). At the site where the pressure is equal to  $P_{msf}$  the large blood volume is indicated by a capacitor [2-4]. This site contains about 70% of total blood volume and has been reported to correspond with the location of the capillaries and post-capillary venules [5]. Resistance over the total systemic circulation ( $R_{sys}$ ) and over the venous system ( $R_v$ ) can be calculated from aortic pressure ( $P_{ao}$ ), central venous pressure ( $P_{cv}$ ) and cardiac output (CO) values as  $(P_{ao}-P_{cv})/CO$  and  $R_v$  by  $(P_{msf}-P_{cv})/CO$ , respectively (Figure 1).  $R_{sys}$  reflects both arterial and venous resistance:  $R_{sys} = R_a + R_v$ . So,  $R_a = R_{sys} - R_v$ .

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**Figure 1** The circulation model to compute the resistances up-streams ( $R_a$ ) and down-streams ( $R_v$ ) of mean systemic filling pressure ( $P_{msf}$ ). The sum of  $R_a$  and  $R_v$  is equal to total systemic resistance ( $R_{sys}$ ). Aortic pressure ( $P_{ao}$ ) and central venous pressure ( $P_{cv}$ ) are measured. Mean systemic filling pressure is determined with inspiratory hold manoeuvres.



In this study we used a hemodynamic condition of hypovolemia as well as dobutamine as a known cardiovascular stimulant to test our model in an intact anesthetized piglet model. In the vasculature, Ruffolo and colleagues [6] presumed that with dobutamine, the  $\beta_2$  mediated

effects are counterbalanced by the  $\alpha_1$  activity leading a decreased total peripheral vascular resistance by a reduction of sympathetic tone and arterial vasodilatation. However, since local vascular effects may differ owing to local differences in receptor expression which varies in arteries and vein, one may see either local vasodilatation or vasoconstriction. Presently, no intact-circulation model exists to study differences in systemic arterial and venous resistance. Since we recently validated a bedside technique to estimate mean circulatory filling pressure (Pmsf) [7], we are now able to determine the venous resistance in patients. Thus, examining both total blood flow and the ratio of the systemic to venous resistance one can quantify the effect of different hemodynamic conditions and vasoactive agents on total systemic vascular resistance and venous resistance.

The aim of our study was to determine the reproducibility of Pmsf, Rsys and Rv in our intact *in vivo* piglet model and, secondly, we tested our model during dobutamine and hypovolemia. We hypothesize that dobutamine would increase CO by the combined actions of increasing inotropy, arterial vasodilatation, with less evident venodilation. Furthermore, we expected both hypovolemia and dobutamine to decrease Pmsf and hypovolemia to not change in the site of Pmsf, i.e. the ratio Rv/Rsys to be constant.

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## Methods

All experiments were performed according to the “Guide for Care and Use of Laboratory Animals” published by the US National Institutes of Health and were approved by the local Animal Care Committee.

### *Surgery*

Ten Yorkshire piglets were anesthetized with 30 mg·kg<sup>-1</sup> sodium pentobarbital intraperitoneal, followed by a continuous infusion of 9.0 mg·kg<sup>-1</sup>·h<sup>-1</sup>. After tracheostomy, the animals were ventilated at a rate of 10 breaths per minute at an I:E-ratio of 2.4:3.6 and with a tidal volume adjusted to maintain arterial PCO<sub>2</sub> of approximately 40 mmHg, while a positive end-expiratory pressure of 2 cmH<sub>2</sub>O was applied. PCO<sub>2</sub>, airway pressure and airflow were measured in the tracheal cannula. The animals were placed in a supine position on a thermo-controlled operating table (38° C). A catheter was inserted through the right common carotid artery into the aortic arch to measure Pao and to sample arterial blood. Two other catheters were inserted through the right external jugular vein. A pulmonary artery catheter was inserted to measure pulmonary artery pressure, to measure thermodilution cardiac output (COtd) and to sample mixed venous blood. A quadruple-lumen catheter was inserted into the superior vena cava to measure Pcv and to infuse sodium pentobarbital and pancuronium bromide (Organon N.V., Boxtel, the Netherlands). The catheters for vascular

pressure measurements were kept patent by an infusion of saline with 2.5 IE Heparin ml<sup>-1</sup> at 3 ml · h<sup>-1</sup>. The bladder was cannulated trans-abdominally to check urine loss in order to maintain water balance. After an intercostal thoracotomy in the second left intercostal space, an electromagnetic flow probe (type transflow 601, model 400, Skalar, Delft, The Netherlands) was placed within the pericardium around the ascendant part of the aortic arch to measure aortic blood flow. Two suction catheters, one dorsal and one ventral, were inserted into the left pleural space. The thorax was closed airtight and both air and fluids were evacuated for 1-2 minutes with -10 cmH<sub>2</sub>O suction while applying a PEEP of 10 cmH<sub>2</sub>O. After surgery and while on continuous pentobarbital infusion, the animals were paralyzed with an intravenous infusion of pancuronium bromide (0.3 mg · kg<sup>-1</sup> · h<sup>-1</sup>), after a loading dose of 0.1 mg · kg<sup>-1</sup> in 3 minutes.

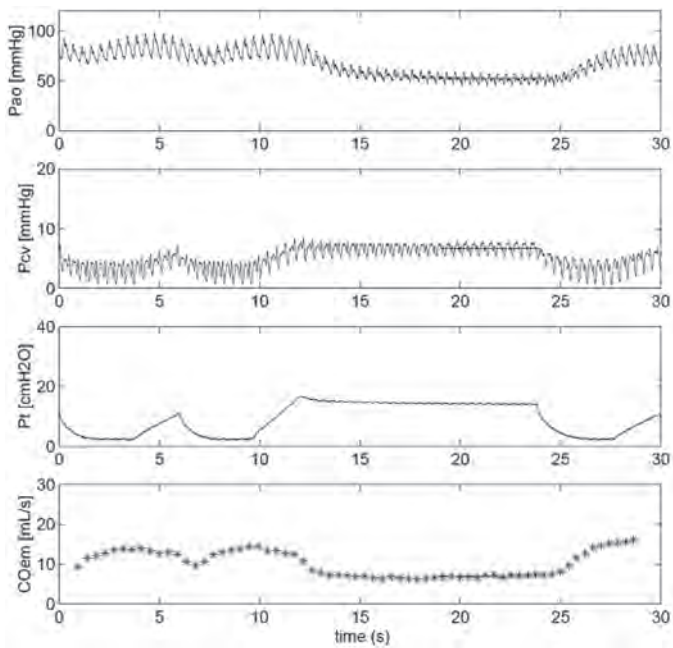
#### *Measurements*

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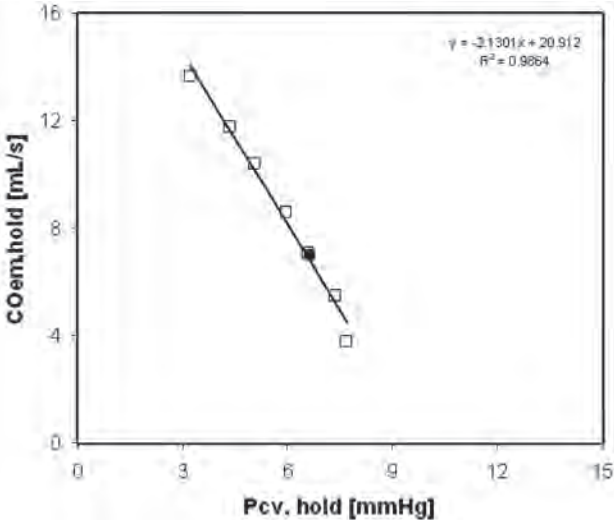
The electrocardiogram (ECG), Pao, pulmonary artery pressure (Ppa), Pcv, flow probe signal and ventilatory pressure (Pvent) were simultaneously recorded. Zero level of blood pressures was chosen at the level of the tricuspid valves, indicated by the pulmonary artery catheter during lateral-to-lateral radiography. The airway pressure transducer was balanced at zero level against ambient air. During the observation periods, ECG, blood flow and pressure signals were sampled in real time for 30-s periods at 250 Hz. The mean of four thermodilution cardiac output measurements equally distributed of the ventilatory cycle was used to obtain the value of COtd<sup>[8,9]</sup>. Areas under the aortic blood flow curves were analyzed online and calibrated by COtd to estimate beat-to-beat cardiac output (COem). After the surgical procedure the animals were ventilated at a rate of 10 min<sup>-1</sup> with an inflation time of 2.4 s and an expiration time of 3.6 s. Tidal volume was readjusted to an end-expiratory PCO<sub>2</sub> of approximately 5.33 kPa (40 mmHg), usually corresponding with a slightly higher arterial PCO<sub>2</sub>. The ventilatory settings were kept constant during the observation periods. We determined Pmsf using inspiratory pause procedures as previously described<sup>[5,10,11]</sup>. Briefly, during inflation of the lungs venous capacitance is loaded due to an increase in Pcv, which leads to a transient reduction in venous return, in right ventricular output and consequently in left ventricular output (Figure 2). To avoid transiently effects on the relationship between venous return and Pcv, we measured Pcv and (CO) during short periods of end-inspiratory steady state following these initial non-steady state conditions. CO and Pcv are determined over the final 5 seconds for a set of seven 12-sec inspiratory hold procedures at seven randomly applied tidal volumes between 25 and 300 ml. The inspiratory hold manoeuvres are separated by 5-minute intervals to re-establish the initial hemodynamic steady state. From the steady state values of Pcv and CO measured by an electromagnetic flow probe (COem) during the seven inspiratory pause periods a venous return curve was

constructed by fitting a linear regression line according to the method of least square means through these data points (Figure 3). Pmsf is defined as the extrapolation of this linear regression to zero flow [5,10,11].

**Figure 2** Effects of an inspiratory hold maneuver on aortic pressure (Pao), central venous pressure (Pcv), airway pressure (Pt) and beat to beat cardiac output (COem). Preceding the hold maneuver the effects of a normal ventilatory cycle are plotted.



**Figure 3** Venous return curve for an individual animal. The relationship between venous return (COem) and central venous pressure (Pcv) is plotted. Mean system filling pressure (Pmsf) is indicated by extrapolating the curve to COem=zero.



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*Protocol*

To eliminate the effects of surgery, opening of the pericardium, and applying mechanical ventilation on the hemodynamic measurements, the piglets were allowed to stabilize for 60 to 120 minutes after surgery. Data collection started once heart rate (HR), mean Pao and Pcv were stable for at least 15 minutes. After stabilization, baseline-1 measurements were performed. Next, continuous dobutamine infusion was started with 6  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and hemodynamic measurements were performed after 30 minutes. The dobutamine infusion was stopped and after 30 minutes baseline-2 measurements were obtained. The observations were continued 15 minutes after bleeding the animals with 10  $\text{ml} \cdot \text{kg}^{-1}$ . The observations ended with baseline-3 measurements 15 minutes after giving back the withdrawn 10  $\text{ml} \cdot \text{kg}^{-1}$  blood.

*Data analysis and statistics*

We fitted the set of seven data points of Pcv and COem by linear regression for each condition to define the venous return curve. We defined Pmsf as the extrapolation of this

linear regression to zero flow (Figure 3), assuming that airway pressure does not affect Pmsf. We have previously validated this extrapolation in piglets [5,10,11]. Total systemic vascular resistance (Rsys) was calculated as the ratio of the pressure difference between mean Pa and mean Pcv and COtd ( $R_{sys} = (Pa - P_{cv})/CO_{td}$ ). The resistance downstream of Pmsf was taken to reflect the resistance to venous return (Rv) and was calculated as the ratio of the pressure difference between Pcv and Pmsf and COtd ( $R_v = (P_{msf} - P_{cv})/CO_{td}$ ). Systemic arterial resistance (Ra) was taken to be the difference between systemic and venous resistance. The ratio of Rv and Rsys describes the location within the circulation where Pmsf exists. A higher ratio implies a more upstream Pmsf location. After confirming a normal distribution of data with the Kolmogorov-Smirnov test, differences in parameters during baseline and interventions were analyzed using paired t-tests. Repeatability was calculated from the three baseline conditions using Bland-Altman analysis. Hereto, for each animal the mean and difference of the values of baseline-1 and 2 and of baseline-2 and 3 was determined. The upper and lower limits of agreement were calculated as bias  $\pm$  2SD. The coefficient of variation (COV) was calculated as  $100\% \times (SD/mean)$ . Effects of time on our data set were calculated by comparing baseline values. Changes induced by the interventions with dobutamine and hypovolemia were compared to the mean of the baseline values before and after the interventions to illuminate time effect. All values are given as mean  $\pm$  SD. A p value  $< 0.05$  was considered statistically significant.

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## Results

Ten 8–10 week old piglets (all females) bodyweight of  $10.3 \pm 0.7$  kg were studied. Pooled data are shown in Table 1. A Kolmogorov-Smirnov test indicated normal distribution of all data. In 10 animals baseline-1, dobutamine, and baseline-2 data was obtained, in only 8 animals we were able to study the effects of bleeding by  $10 \text{ ml} \cdot \text{kg}^{-1}$ .



**Table 1** Pooled results for 10 piglets at start (Baseline-1), 30 minutes after the start of 6  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  IV dobutamine infusion (Dobutamine), 30 minutes after stopping the dobutamine infusion (Baseline-2), 15 minutes after bleeding 10  $\text{ml} \cdot \text{kg}^{-1}$  (hypovolemia) and 15 minutes after reestablishing normovolemia (Baseline-3).

	Baseline-1	Dobutamine	Baseline-2	Hypovolemia	Baseline-3
Pao (mmHg)	88.10 ± 17.24	87.51 ± 9.37	82.56 ± 17.02	83.05 ± 14.46	86.83 ± 18.30
Ppa (mmHg)	15.52 ± 3.51	19.77 ± 6.99	19.74 ± 7.39	17.10 ± 6.51	18.96 ± 5.97
Pcv (mmHg)	4.09 ± 1.33	4.10 ± 1.03	4.62 ± 1.38	3.75 ± 1.71 †	4.69 ± 1.47
HR (min <sup>-1</sup> )	146 ± 42	215 ± 33 ‡	152 ± 42	175 ± 47 ‡	150 ± 45
COTd (ml · sec <sup>-1</sup> )	24.15 ± 3.70	33.64 ± 3.94 ‡	24.53 ± 5.38	22.69 ± 3.87 †	24.57 ± 4.64
Pmsf (mmHg)	13.59 ± 1.04	12.02 ± 1.27 †	14.10 ± 1.37	10.94 ± 1.81 ‡	14.85 ± 1.28
Pvr (mmHg)	10.71 ± 1.21	7.88 ± 1.12 *	9.50 ± 1.72	7.19 ± 1.66 ‡	10.15 ± 1.75
Rv (mmHg · sec · ml <sup>-1</sup> )	0.401 ± 0.095	0.237 ± 0.037 ‡	0.406 ± 0.126	0.327 ± 0.104 †	0.465 ± 0.085
Rsys (mmHg · sec · ml <sup>-1</sup> )	3.474 ± 0.424	2.507 ± 0.271 ‡	3.379 ± 0.322	3.496 ± 0.352	3.359 ± 0.455
Rv / Rsys	0.117 ± 0.031	0.096 ± 0.019 †	0.127 ± 0.037	0.095 ± 0.035 †	0.129 ± 0.039
Hb (g · dL <sup>-1</sup> )	9.56 ± 1.02	10.34 ± 1.22 †	9.73 ± 0.99	9.67 ± 0.89	9.71 ± 1.05

Aorta pressure (Pao), pulmonary artery pressure (Ppa), central venous pressure (Pcv), heart rate (HR), cardiac output with thermomodulation (COTd), mean systemic filling pressure (Pmsf), pressure gradient for venous return (Pvr), venous flow resistance (Rv), systemic flow resistance (Rsys), location of Pmsf (Rv/Rsys), and hemoglobin (Hb).  
 \*  $p < 0.05$ , †  $p < 0.01$  and ‡  $p < 0.001$  to the average of the baseline value before and after the intervention.

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### Repeatability

Bland-Altman analyses for repeated measurements of the main derived variables Pmsf, Pvr, Rsys, Rv and Rv/Rsys are given in Table 2. A remarkable low percentage coefficient of variation of 3.8% was found for Pmsf. The percentage coefficient of variation increases with the number of variables incorporated in the calculation and was highest for Rv/Rsys.

**Table 2** Bland-Altman results for repeated measurements of mean systemic filling pressure (Pmsf), gradient for venous return (Pvr), systemic vascular resistance (Psys), the resistance for venous return (Rv) from Pmsf to central venous pressure and the quotient Rv/Rsys as a location of Pmsf in the circulation. Data of baseline-1, baseline-2 and baseline-3 are used (n=18).

	Mean	Bias	SD	COV %	limits of agreement	
					lower	upper
Pmsf (mmHg)	14.17	-0.55	0.54	3.8	-1.63	0.53
Pvr (mmHg)	9.64	-0.18	0.78	8.1	-1.74	1.38
Rsys (mmHg · sec · ml <sup>-1</sup> )	3.422	0.078	0.348	10.0	-0.618	0.774
Rv (mmHg · sec · ml <sup>-1</sup> )	0.415	-0.023	0.059	14.2	-0.141	0.095
Rv/Rsys	0.12	0.01	0.02	16.7	-0.03	0.05

### *Interventions*

The infusion of  $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  dobutamine increased HR and COtd and decreased Pmsf, Pvr, Rv, Rsys and Rv/Rsys ratio. Whereas Pao, Ppa and Pcv did not change during the study. The decrease of Rv during dobutamine was larger than the decrease in Rsys, 52% and 28% respectively. Recovery baseline condition after dobutamine (baseline-2) did not show any significant changes from the initial baseline values (baseline-1), except for HR which decreased after dobutamine infusion was stopped but still was elevated compared to baseline-1. Bleeding the animals with  $10 \text{ ml} \cdot \text{kg}^{-1}$  showed a decrease in Pcv, Pmsf, Pvr, Rv and Rv/Rsys. Recovery to baseline condition after bleeding (baseline-3) did not show any significant changes from baseline values before bleeding (baseline-2). Surprisingly, hemoglobin (Hb) increased during continuous dobutamine infusion and returned to baseline-1 values 30 minutes after the infusion was stopped. Hemoglobin did not change by bleeding.

### **Discussion**

Our data supports the feasibility to estimate Pmsf, Rsys and Rv. The discrimination between arterial and venous resistance is possible because we can estimate Pmsf accurately. Our data on vascular resistance clearly shows that although both arterial and venous components of vascular resistance decrease, the primary peripheral vascular effects of dobutamine in the healthy animal model was to induce more venodilation than arterial dilation. Bleeding the animals showed Pmsf, Pcv, COtd and surprisingly Rv to decrease and Pao and Rsys to be constant. Evidently, there is some compensation for the loss of venous return by adaptation of Rv.

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### *Repeatability*

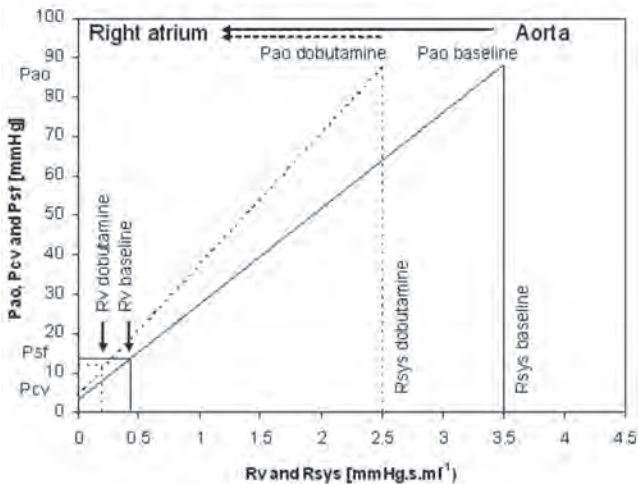
Comparison of baseline-1, -2 and -3 showed no differences, except for the observation of heart rate HR during baseline-2. Therefore, we conclude for a stable observation periods in our animals. We determined the precision of the main derived variables, i.e. Pmsf, Pvr, Rsys and Rv, by Bland-Altman analysis of repeated measurements (Table 2). Although, Pmsf is determined by extrapolation of the venous return curve to COem is equal to zero (Figure 3), the coefficient of variation appeared to be surprisingly low (3,8%). With the low coefficient of variation for Pmsf, Rv and Rsys changes by the intervention with dobutamine and hypovolemia can be monitored with precision. Therefore, we consider the data as presented in Table 1 as reliable.

Our estimated Pmsf values (11-15 mmHg) are in agreement with those described in highly instrumented animals, which are in dogs 7-12.5 mmHg [12-17], rats 7-9 mmHg [18,19], pigs 10-12

mmHg [5,10,11], and as high as 20-30 mmHg in conscious calves implanted with an artificial heart [20]. Furthermore, we report a baseline Pmsf value of 19 mmHg in cardiovascular surgical patients [7].

How can our data be explained? In a non-controlled circulation a decrease in effective blood volume (i.e. a change from stressed to unstressed volume) will be reflected by a decrease in Pmsf [21]. If dobutamine caused arterial vasodilation such that the number of perfused capillaries increased, then unstressed volume should also increase, decreasing Pmsf for a constant blood volume. The greater number of draining venous conduits would also decrease the resistance to venous return. We found that dobutamine decreased without altering Pcv, decreasing the pressure gradient for venous return. Despite this decrease in pressure gradient, cardiac output was increased. Thus, the decrease in Rv was more than inversely proportional to the increase in cardiac output or cardiac output would have remained constant. A decrease in Rv may be caused by four mechanisms; (1) a decrease of the length of the vascular bed between the sites where the pressure is equal to Pmsf and right atrium, (2) an increase in cross section of the vascular bed, (3) decrease blood viscosity of blood or (4) a combination of the three mechanisms. As we measure an increase in Hb during dobutamine infusion a decrease in viscosity is very unlikely. Thus, the observed decrease in Pmsf combined with the increased COtd requires that Rv decrease due to an increase in the venous flow cross-sectional area, presumably due to dobutamine-induced increased parallel vascular blood flow.

**Figure 4** Conceptual model of the systemic circulation. Horizontally, the linear projection of vascular flow resistance ( $R_{sys}$ ) between aortic valves (at the right) and right atrium (at the left) is plotted. In this linear projection the aorta takes about 2%, the arterioles about 55%, the remaining arterial system about 15% and the rest is distributed between capillaries and the venous system. The resistance ( $R_v$ ) down-streams mean systemic filling pressure ( $P_{sf}$ ) and central venous pressure ( $P_{cv}$ ) is indicated. Vertically, aortic pressure ( $P_{ao}$ ), central venous pressure ( $P_{cv}$ ) and mean systemic filling pressure for baseline condition and during infusion of dobutamine are plotted. The values of Table 2 are used to construct the model. Further explanation is given in the text.



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The changes in  $P_{ao}$ ,  $P_{cv}$ ,  $COTd$ ,  $R_{sys}$  and  $R_v$  are illustrated schematically in Figure 4, in which flow resistance is projected on the x-axis. We have used this graphical model to analyze two different stationary conditions in circulation, i.e. baseline condition and during infusion of dobutamine. The numeric data for this model are taken from Table 1, columns baseline-1 and dobutamine. The lines between  $P_{ao}$  and  $P_{cv}$  represent the pressure gradient ( $P_{sys}$ ) over  $R_{sys}$  and between  $P_{msf}$  and  $P_{cv}$ ; the pressure gradient ( $P_{vr}$ ) for venous return over  $R_v$ . The slope of the lines represent blood flow, i.e.  $COTd = P_{sys}/R_{sys} = P_v/R_v$ . During dobutamine infusion the  $P_{ao}-P_{cv}$  difference was equal to baseline. However,  $COTd$  increased and both  $R_{sys}$  and  $R_v$  decreased significantly. The fall in  $R_v$  due to dobutamine was larger than the fall in  $R_{sys}$ , 52% and 28% respectively. From this difference in response to dobutamine we conclude that the primary peripheral vascular effect of dobutamine is on the venous side of the circulation as

shown in Figure 4. The larger decrease on the venous side can be explained mainly by the decrease in Pmsf due to dobutamine. If we had observed no change in Pao, Pcv or Pmsf despite an increase in COtd, then Rv must have changed proportional to Rsys, which is described by the intersection of dashed Pao-Pcv dobutamine line and solid Pmsf line. Importantly, our method to determine Pmsf has recently also been validated in mechanically ventilated patients [7], thus this approach can now be applied to humans as well. In addition, we confirmed the well-known positive inotropic effect of dobutamine as manifest by the increase in HR and stroke volume despite an unchanged Pcv and Pao. It is unclear from our data which factor plays a greater role in increasing COtd, increasing inotropy or decreasing Rv. In our animals hypovolemia caused/produced Pmsf, Pcv, COtd and surprisingly Rv to decrease and Pao and Rsys to be constant. The gradient for venous return,  $Pvr=Pmsf-Pcv$ , decreased with 27%, so with a constant resistance for venous return, Rv, we expected a decrease in CO of the same order ( $CO=Pvr/Rv$ ). However, Rv decreased by 16% leading to a decrease in COtd with only 9%. Thus, there appears to be compensation for the loss of venous return by adaptation of Rv, manifested by the significant increase in heart rate. Potentially, this occurred by shifting blood away from the splanchnic circulation with its higher Rv to other systemic vascular circuits, as we have previously shown [22], but our study does not allow us to confirm this speculation. However, since we observed that the location at which Pmsf exist ( $R_s/R_{sys}$ ) shifted more into the direction of the venous site of the circulation, suggests that such a redistribution of blood flow did occur.

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### *Limitations*

Some limitations apply to our model. The technical set-up with a flow probe around the aorta is not general applicable in humans. A reliable less invasive beat-to-beat determination of cardiac output by trans-oesophageal ultrasound or arterial pulse contour allow similar studies to be done in humans [7].

We measured only Pao and Pcv and calculated Pmsf. Pmsf is a lumped variable of all the vascular beds. Thus, it is not clear, which specific or general vascular beds were affected by dobutamine infusion or hypovolemia. The difference in local adrenergic receptor (subtype) expression and overall expression of the receptors vary between different vascular beds and between species. Although the circulation of the pig bares macroscopic resemblance to the human physiology, a direct extrapolation of the results is precarious. This, however, also applies for previous studies [1,6]. Clearly, future human studies using less invasive means will need to be done to validate these findings in patient with normal vascular responsiveness and disease.

## Conclusions

The use of our *in-vivo* animal model to assess the hemodynamic effects on Pmsf, Rsys, Rv and Rv/Rsys of a cardiovascular drug and of hypovolemia was successfully tested. The discrimination between arterial and venous resistance is possible because we can estimate Pmsf accurately. The higher cardiac output seen during dobutamine infusion was attributed to the combined increased cardiac function and decreased venous flow resistance despite a decrease in Pmsf. Hypovolemia decrease as expected Pmsf but this decrease was partly compensated for by a decrease in Rv to preserve venous return and thus cardiac output.

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